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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,723	11/29/2005	Toshihiro Tanaka	P26633	1079

7055 7590 12/10/2009

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,723	TANAKA ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-11 and 13-32* is/are pending in the application.

4a) Of the above claim(s) *4,10,11 and 13-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3 and 5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/27/2009, 10/20/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 8/27/2009.

2. Claims 3-11, 13-32 are pending. Claims 1-2 and 12 have been cancelled.

3. Claims 4, 10-11 and 13-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/09/2007 and the restriction has been made FINAL.

4. The following rejections for claims 3 and 5-9 are reiterated. Response to arguments follows.

5. This action is FINAL.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 8/27/2009 and 10/20/2009 have been considered by the examiner. It is noted that the office action Japanese patent application No. 2004527375 has been considered, however, no English translation has been provided.

Claim Rejections - 35 USC § 112/Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 3 and 5-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method of determining myocardial infarction in a human comprising detecting a homozygous A allele at the nucleotide 80 of SEQ ID No. 3 wherein a homozygous A allele is indicative of myocardial infarction does not reasonably provide enablement for determining any arteriosclerotic disease in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

Claim 3 is drawn to a method for determining a increased risk of arteriosclerotic disease comprising detecting SNP C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID no. 3 (referred to as C723A or

T26N or Thr26Ala). Claim 5 is drawn to a method for determining a vascular inflammatory disease which comprises detecting a gene polymorphism whereby there is an amino acid change from threonine to asparagine. Claim 6 defines the disease as myocardial infarction. Claim 7 is defines the SNP position in Claim 3. Claims 8 and 9 define the method of detection and SNP position in Claim 3.

The claims are broadly drawn to determining any vascular inflammatory disease by detection of a C or an A at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID no. 3.

When the claims are read in light of the specification, the specification does not provide predictable guidance for any arteriosclerotic by detection of a C or an A at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID no. 3. The art, as presented below, teaches that such correlations of polymorphism and disease are disease specific.

Nature of the Invention

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification discloses that LT-α gene is one of the cytokines produced during the earliest phase of the process of angiitis and it activates the cytokine cascade

by inducing other mediators (p. 2 2nd paragraph). The specification discloses that these mediators are known to be involved in atheroma formation and aterma lesions (p. 2 2nd paragraph).

The specification discloses a method for determining inflammatory diseases involving identifying gene polymorphism associated with the disease (p. 3 2nd paragraph). The specification discloses that the invention has typed SNPs within a population of about 1000 myocardial infarction patients and a control group of about 1000 persons by multiplex PCR-invader assay (p. 3 3rd paragraph). However, the specification has not provided a predictable correlation of a specific SNP with any arteriosclerotic disease.

The specification discloses that the A polymorphism at nucleotide 80 of the nucleotides sequence of exon 3 of the LT-α gene shown in SEQ ID No. 3 causes an amino acid mutation from threonine to asparagine in codon 26 (p. 13 1st full paragraph). However, this mutational change has not been correlated with any arteriosclerotic disease. The specification asserts a correlation between the specific SNP and myocardial infarction. However, the art, as presented below teaches that correlation between a specific type of arteriosclerotic and the specific SNP cannot be extrapolated to any arteriosclerotic (see Asselbergs et al.). Further the claims are drawn to detection of a C or an A, however, the instant specification discloses associations to the homozygous A allele and not to the C at position 80.

The specification does not define the term " arteriosclerotic". The specification provides examples of arteriosclerotic such as myocardial infarction and cerebral

apoplexy (p. 13 last paragraph). The art teaches that arteriosclerotic as the hardening and thickening of the walls of the arteries. Arteriosclerosis can occur because of fatty deposits on the inner lining of arteries (atherosclerosis), calcification of the wall of the arteries, or thickening of the muscular wall of the arteries from chronically elevated blood pressure (www.medterms.com). The art teaches that there are various types of arteriosclerotic diseases such as atherosclerosis, coronary artery disease, and peripheral arterial disease (Types of atherosclerosis www.wrongdiagnosis.com). This broad disease group includes a genetically diverse set of diseases. Asselbergs et al., as present below, teaches that not all types of arteriosclerotic disease are associated with the claimed SNP. It would be unpredictable to extrapolate one specific disease association to any arteriosclerotic disease because as shown by the art each disease is genetically different.

In summary, the claims are drawn to determining any arteriosclerotic disease. The specification however only discloses the correlation of one arteriosclerotic disease, myocardial infarction. The art, as discussed below, teaches that extrapolation of one correlation between a specific disease and a specific SNP to other diseases is unpredictable. Therefore the skilled artisan would have to perform a large amount of experimentation in order to correlate the particular in the LT-A gene to any arteriosclerosis disease. There would be many intervening steps the skilled artisan would have to perform without any guarantee of success to practice the invention as claimed.

Working Examples

The specification provides a Japanese population in which 1133 patients have been diagnosed with myocardial infarction (p. 23 last paragraph. P. 24 1st paragraph). The specification asserts that SNP were detected using the invader PCR assay method (p. 24).

The specification asserts that 94 myocardial infarction patients were genotypes and the allelic frequency was compared to a population of healthy subjections (p. 26 1st paragraph). 26 SNPs were types and expanded by sample size (p. 27 1st paragraph). Table 1 indicates a sample size of 1133 myocardial infarction patients and 1006 control patients. The specification asserts that the population was genotyped (table 1).

Therefore the specification teaches that of the 26 SNPs detected on 1133 myocardial infarction patients only 3 SNPs in LT-A had a statistically significant association. For SNP C723A there are three possible genotypes (CC, CA, and AA) (e.g. the claimed SNP) (Table 1). The specification discloses that there is a predictable correlation of homozygous (AA) individuals with myocardial infarction compared to homozygous wild type (CC) and heterozygous (CA). Therefore the p-value discloses in Table 1 is based on the detection of the "A" allele on both strands of nucleic acid. The claims, however, are encompass detecting one "A" allele. Therefore it is unpredictable that there is a correlation of the allelic mutation based on the correlation of the homozygous AA in the population.

The predictability or unpredictability of the art and degree of experimentation

Asselbergs et al. (Clinical Science 2007 Vol 112 p. 291) teaches the detection of C804A (e.g. the same SNP which is claimed in the pending claim set). Asselbergs et al. teaches that with regard to coronary heart disease and the detection of the SNP there was no association (abstract). Coronary heart disease is a type of arteriosclerosis heart disease and as such Asselbergs et al. teaches there is no association between the claimed SNP and a particular type of arteriosclerotic disease. As such the claims encompass an association of any arteriosclerotic disease with detection of a particular SNP however, the instant specification only provides an association in one type of arteriosclerotic disease and the art teaches that other types of arteriosclerotic diseases are not associated.

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to correlate determination of any arteriosclerotic disease with detection of the specific SNP in the LT-A gene.

The specification discloses a method of detecting many SNPs from LT-A and correlating the mutations to one specific inflammatory disease (myocardial infarction). The specification teaches that only 3 of the SNPs tested were statistically correlated to myocardial infarction.

The art teaches that associations between mutations of LT-A gene and arteriosclerotic disease are unpredictable and population specific (e.g. see the teaching of Asselbergs et al.). The art teaches that even the mutation T26N (the elected SNP) is not correlative to CHD (e.g. a particular type of arteriosclerotic disease).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written.

The skilled artisan would have to analyze the association of the elected SNP to determine its association with any arteriosclerotic disease. However, neither the specification nor the art provides guidance as to extrapolate a correlation of a specific disease to any arteriosclerotic disease. The skilled artisan would then need to test associations in a variety of populations because the art teaches that associations are population specific.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of

guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide a predictable correlation of detection of the SNP C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 as shown in SEQ ID No. 3 to any arteriosclerotic disease. Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is provided below with response to arguments following.

(A) The reply notes that the claims have been amended to be drawn to an increase risk of arteriosclerotic disease (p. 8 4th paragraph).

It is noted that the claims therefore have been interpreted as correlating the presence of the polymorphisms to increased risk and not any risk of arteriosclerotic.

(B) The reply asserts that the specification does not provide enablement for every arteriosclerosis disease given that myocardial infarction is within the scope of

arteriosclerotic diseases (p. 9 1st paragraph). The reply asserts that the specification states an increased risk of arteriosclerosis disease can be determined in humans by detecting a C/A polymorphism (p. 9 1st full paragraph). The reply asserts that unless there is a reason to doubt the objective truth of the statements in the specification, these statements must be relied on for enabling support (p. 9 1st full paragraph).

The reply asserts that the reference of Asselbergs et al. relied upon by the examiner is not sufficient to show lack of enablement (p. 9 last paragraph). The reply asserts that although Asselberg et al. teaches that there was no association of the SNP and coronary heart disease that the Asselbergs et al. reference actually discloses that there was no association to myocardial infarction (p. 9 last paragraph to p. 10 1st paragraph). The reply asserts that this is contrary to the scope given in the office action (p. 10 1st paragraph).

The reply asserts that the specification and the PROCARDIS study (provided in a previous response) disclose why the Asselbergs' findings are inconsistent with the present invention. The reply asserts that the PROCARDIS study uses a large heterogeneous Caucasian population whereas the Asselbergs study used an homogenous Japanese population (p. 10 2nd paragraph). The reply asserts that the PROCARDIS study states that there the haplotype LTA 252G/N26 defined by at least three functional SNPS may be related to myocardial infarction and/or coronary artery disease (p. 10 last paragraph). The reply asserts that there is nothing in the Asselbergs study that indication why the PROCARDIS study is incorrect (p. 11 2nd full paragraph). The reply asserts that the PROCARDIS study rebuts the findings of Asselbergs and the

reply asserts that when the appropriate types of tests are used on the appropriate sample group the association of the LTA SNP and arteriosclerotic disease is observed (p. 11 2nd full paragraph). The reply asserts that the office has not provided any reason that the PROCARDIS study is flawed or incorrect (p. 11 3rd full paragraph).

These arguments have been fully considered but have not been found persuasive.

Although, it is acknowledged that the statements provided in the specification must be taken as objective truths, in the instant case the statements provided in the specification has not provided enabling support. First, it is noted that both the statement recited by the reply on p. 9 2nd paragraph and the claims are drawn to detection either a C or an A and correlation to the presence of arteriosclerosis disease. This is not supported by the specification as the specification discloses it is the detection of the homozygous A allele which is correlative to MI. Therefore the breadth of the statement and the claim encompass correlations which are not enabled. Specifically the specification does not disclose that the presence of the C allele is correlative, but rather only the A allele.

Further, the reply asserts that the population studied by Asselbergs et al. is drawn to populations with myocardial infarction which is the same scope as provided by the Scope of enablement. However, based upon the reading of the reference, it is the examiner's position that this is not the case. The study population of Asselbergs et al. is 249 women and 266 men who have developed non-fatal myocardial infarction or fatal CHD (p. 292 2nd column 1st paragraph of Asselbergs). This population therefore

includes two types of arteriosclerotic disease (myocardial infarction and fatal CHD). Therefore the two types of disease populations differ. The example in the instant specification is drawn to only myocardial infarction whereas Asselbergs population is drawn to a combinatory arteriosclerotic disease group. As such the examiner maintains the position that not all types of arteriosclerosis disease are correlative to a particular polymorphism.

The reply is disputing the Asselbergs reference and asserts that the negative results presented by the reference are based upon population type and test type. The reply points to the PROCARDIS study which shows using a linkage disequilibrium test in a European large scale family that the haplotype of three functional SNPs may be causally related to MI or CAD (p. 10 last paragraph of reply). Herein the reply is comparing the Asselberg reference to a study which associates a haplotype to MI or CAD. However, this is not evidence for the scope of the claims, which is drawn only to the detection of one polymorphism position. The reply has not pointed to the PROCARDIS study and shown that the polymorphisms position is correlative, but rather only has shown a haplotype analysis. Therefore it is not clear if the same associations in the PROCARDIS study would be made using only the detection of a C or an A at nucleotide 80. As such, the scopes of the reference are not the same as the scope of the claims. Further, the reply has not brought in any evidence showing the same scope as claimed. However, even if the applicant brought in data showing that in the PROCARDIS study there was a predictable association with MI or CAD, this still would not be sufficient by any arteriosclerosis disease as Asselbergs teaches that no

association is present in populations of MI and CHD. Further, the claims are not limited to a particular population or testing type, but rather, any population of humans and the detection of a C or an A. Therefore the evidence presented by the PROCARDIS study is not sufficient to provide support for the claimed method.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

/Sarae Bausch/
Primary Examiner, Art Unit 1634